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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,805	06/05/2001	Jeffrey Wheeler	INEX.P-010	5995

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OPPEDAHL AND LARSON LLP
P O BOX 5068
DILLON, CO 80435-5068

EXAMINER

EPPS FORD, JANET L

ART UNIT PAPER NUMBER

1635

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/875,805

Applicant(s)

WHEELER ET AL

Examiner

Janet L. Epps-Ford, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

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DETAILED ACTION

1. In view of the Appeal Brief filed on 11-20-03, PROSECUTION IS HEREBY REOPENED. A new grounds of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Response to Arguments

2. Applicant's arguments with respect to the rejection of claims 1-14 under 35 USC 102(e) as anticipated by Choi et al. have been considered but are moot in view of the new ground(s) of rejection.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-29 of U.S. Patent No. 5,976,567.

The instant claims are drawn to methods for preventing particle aggregation of lipid:nucleic acid complex particles or preparing a lipid:nucleic acid complex, wherein said methods comprise incorporating a non-cationic lipid into a lipid:nucleic acid complex, wherein the non-cationic lipid is a polyethylene glycol-based polymer. Additionally, the instant claims recite wherein the amount of the non-cationic lipid added to the lipid:nucleic acid complex is from 1 to 15% of the particles, wherein the lipid:nucleic acid complex is lyophilized, and wherein the nucleic acid is linked to an expression vector to facilitate gene expression after entry into a cell.

Claims 14-29 of U.S. Patent No. 5,976,567 ('567') recite a method for the preparation of serum-stable plasmid-lipid particles, comprising contacting non-cationic lipids with coated plasmid-lipid particles, wherein said method comprises adding a polyethylene glycol-lipid conjugate, and further wherein said polyethylene glycol-lipid conjugate is PEG-Ceramide conjugate (see claims 14-17). The method recited in the claims of issued US Pat No. 5,976,567 do not recite wherein the amount of the non-cationic lipid is from 1 to 15% of the particles or wherein the lipid:nucleic acid complex is lyophilized. However, in a preferred embodiment of US Patent No. 5,976,567, col. 25, lines 20-22, of '567 discloses that the concentration of PEG, PEG-ceramide modified lipids in the plasmid:lipid particles will be about 1-15%. Additionally, in another specific embodiment of the '567 patent, col. 25, lines 23-26, the plasmid:lipid

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particles of the invention are preferably lyophilized prior to administration. Therefore, although these specific limitations are not recited in the claims, one of ordinary skill in the art at the time of filing would have been motivated to incorporate these limitations into the claimed invention since these limitations define an obvious variation of the invention claimed in the '567 patent. See MPEP § 804, which states that "[T]hose portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent."

Therefore, the invention as whole would have been *prima facie* obvious over claims 14-29 of US Patent No. 5,976,567.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the presence of a detergent in the first step wherein the cationic lipid is combined with plasmid DNA. According to Applicant's specification, without the presence of a detergent in the step wherein the cationic lipids are mixed with plasmid DNA, the resultant coated plasmids will aggregate and precipitate out of solution. However, the presence of a detergent reduces this aggregation and allows the coated plasmids to react with excess lipids (typically, non-cationic lipids) to form particles in which the plasmid is encapsulated in a lipid bilayer. (See the specification as filed, page 27, 3rd paragraph) Therefore, since the claimed methods to prevent aggregation do not recite the presence of a detergent, the

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claimed methods appear to be incomplete since the presence of the detergent is required to aid in the interaction of the non-cationic lipid, and thereby prevention of aggregation of the lipid-nucleic acid complex particles.

7. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventing particle aggregation of lipid:nucleic acid complex particles and preparing lipid:nucleic acid complexes comprising the use of a detergent in the step for combining nucleic acid and cationic lipids, does not reasonably provide enablement for practicing the claimed method without the presence of the detergent in the first step. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims

8. The instant claims are directed to a method of preventing particle aggregation of lipid:nucleic acid complexes wherein nucleic acid is combined with a cationic lipid to produce a lipid:nucleic acid complex, and mixing the complexes with a polyethylene glycol-based polymer non-cationic lipid, wherein the polyethylene glycol-based polymer reduces the tendency of the lipid:nucleic acid complex to aggregate. However, the specification as filed clearly indicates that once cationic lipids and nucleic acid are mixed together, sticky complexes of cationic lipid and nucleic acid will form aggregates and precipitate, see for example Figure 2 of the instant application. Moreover, page 27, 3rd paragraph, of the specification as filed states that without the presence of a detergent in the step wherein the cationic lipids are mixed with plasmid DNA, the resultant coated plasmids will aggregate and precipitate out of solution. However, the presence of a detergent reduces this aggregation and allows the coated plasmids to react with excess lipids (typically, non-cationic lipids) to form particles in which the plasmid is encapsulated in a lipid

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bilayer. It is apparent from the specification as filed, that in order for the added non-cationic lipid, in the second step in the claimed methods, to function to assist in preventing particle aggregation, the method requires the presence of a detergent to reduce the aggregation associated with the first step and allow the cationic lipid coated nucleic acid to react with excess non-cationic lipids to prevent further particle aggregation and precipitation, and thereby form particles wherein the nucleic acid is encapsulated in a lipid bilayer.

WO 96/40964A1 also teaches the importance of a detergent when combining cationic lipids and plasmid DNA. It teaches that the presence of the detergent prevents aggregation and precipitation of plasmids coated with cationic lipids, and allows the interaction of these complexes with interact with excess non-cationic lipids to form particles in which the plasmid is encapsulated in a lipid bilayer (see page 23, 3rd paragraph). It is also noted that if the coated plasmids are not encapsualted they are potentially exposed to nucleases that would degrade the plasmid DNA (see page 23, 1st paragraph).

The specification as filed does not teach any other method for preventing particle aggregation or preparing lipid: nucleic acids other than a method incorporating the use of a detergent when combining cationic lipids and nucleic acids. Additionally, the specification as filed does not provide any prior art reference that would support practicing the claimed methods without the presence of the detergent in the first step of the claimed methods. Since it does not appear that one skilled in the art would be able to readily anticipate what other factors, other than the presence of a detergent, could be used to prevent particle aggregation in the first step, or predict the effect of such a change in the claimed methods, then there appears to be lack of predictability in the art in this regard. In order to practice the full scope of the claimed methods

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which encompass practicing the claimed invention without the use of a detergent in the first step, the skilled artisan would have to resort to de novo experimentation in order to determine methods to overcome the aggregation and precipitation of the cationic lipid: nucleic acid complexes such that a sufficient amount of non-cationic lipid may interact with the cationic lipid and nucleic acid in order to form lipid:nucleic acid complexes, wherein the non-cationic lipid functions to prevent particle aggregation of said complexes.

Therefore, in light of the limited guidance provided by the specification in regards to practicing the claimed methods without the inclusion of a detergent in the first step, and the unpredictability associated with devising new methods to overcome particle aggregation and precipitation in the first step, it is concluded that skilled artisan would have to resort to undue experimentation in order to practice the full scope of the claimed invention.

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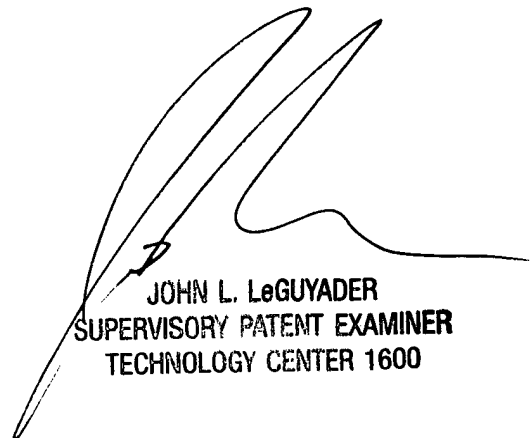
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE



JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600